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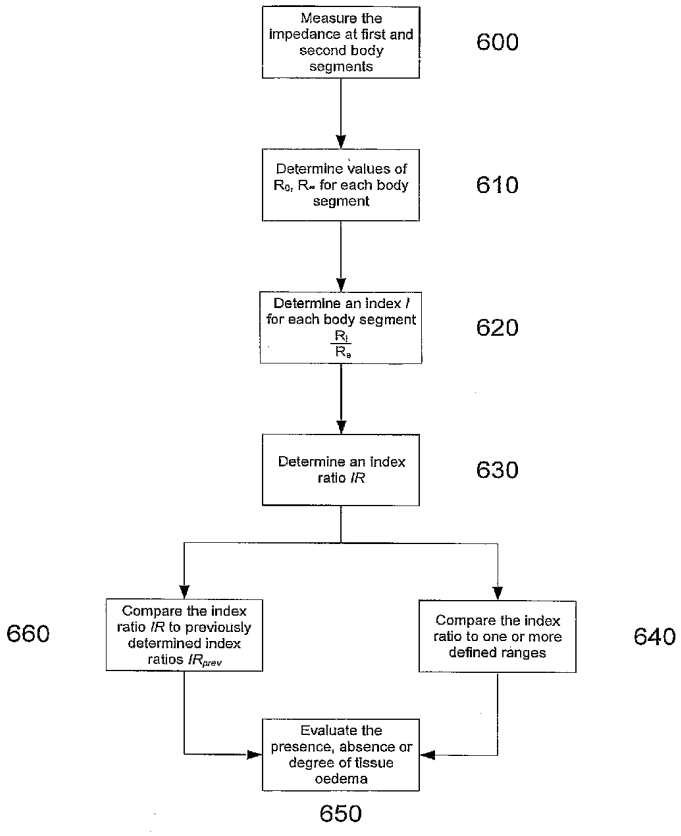

(57) Abstract: A method of detecting tissue oedema in a subject. The method includes determining a measured impedance for first and second body segments. An index indicative of a ratio of the extra-cellular to intra-cellular fluid is then calculated for each body segment, with these being used to determine an index ratio based on the index for the first and second body segments. The index ratio can in turn be used to determine the presence, absence or degree of tissue oedema, for example by comparing the index ratio to a reference or previously determined index ratios.

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OEDEMA DETECTION

Background of the Invention

The present invention relates to a method and apparatus for detecting tissue oedema, and in particular, to a method and apparatus for detecting tissue oedema using impedance measurements.

Description of the Prior Art

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that the prior art forms part of the common general knowledge.

Lymphoedema is a condition characterised by excess protein and oedema in the tissues as a result of reduced lymphatic transport capacity and/or reduced tissue proteolytic capacity in the presence of a normal lymphatic load. Acquired, or secondary lymphoedema, is caused by damaged or blocked lymphatic vessels. "The commonest inciting events are surgery and/or radiotherapy. However, onset of lymphoedema is unpredictable and may develop within days of its cause or at any time during a period of many years after that cause.

WO00/79255 describes a method of detection of oedema by measuring bioelectrical impedance at two different anatomical regions in the same subject at a single low frequency alternating current. The two measurements are analysed to obtain an indication of the presence of tissue oedema by comparing with data obtained from a normal population.

Other known methods of analysis of bioelectrical impedance measurements involve determining a phase and amplitude value for the measured signals. The measurement of amplitude is straightforward but the measurement of phase is more complicated and therefore the required equipment is costly.

Summary of the Present Invention

In a first broad form the present invention provides a method of detecting tissue oedema in a subject, the method including, in a processing system:

a) determining a measured impedance for first and second body segments;

b) for each body segment, and using the measured impedance, determining an index indicative of a ratio of the extra-cellular to intra-cellular fluid;

c) determining an index ratio based on the index for the first and second body segments;

d) determining the presence, absence or degree of tissue oedema based on the index ratio.

Typically the method includes, in the processing system:

a) comparing the index ratio to at least one reference; and,

b) determining the presence, absence or degree of tissue oedema based on the results of the comparison.

Typically the reference includes at least one of:

a) a predetermined threshold;

b) a tolerance determined from a normal population; and,

c) a predetermined range.

Typically the reference includes an index ratio previously determined for the subject.

Typically the previously determined index ratio is determined prior to the subject undergoing at least one of:

a) surgery; and,

b) treatment.

Typically the first and second body segments are different types of body segment.

Typically the first and second body segments are limbs.

Typically the first body segment is a leg and the second body segment is an arm.

Typically the method includes, in the processing system:

a) determining a plurality of measured impedances for each body segment, each measured impedance being measured at a corresponding measurement frequency; and,

b) determining the index ratio based on the plurality of measured impedances.

Typically the method includes, in the processing system:

a) determining values for parameters R_0 and R_∞ from the measured impedance values; and,

b) calculating the index (I) using the equation:

$$I = \frac{R_\infty}{R_0 - R_\infty}$$

where:

R_0 is the resistance at zero frequency; and,

R_∞ is the resistance at infinite frequency.

Typically the method includes, in the processing system, determining the parameter values using the equation:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$

where:

Z is the measured impedance at angular frequency ω,

τ is a time constant, and

α has a value between 0 and 1; and

Typically the method includes, in the processing system:

a) determining the impedance of each body segment at four discrete frequencies; and,

b) determining values for the parameters by solving the equation using four simultaneous equations.

Typically the method includes, in the processing system, determining the parameter values by:

a) determining an impedance locus using the measured impedance values; and,

b) using the impedance locus to determine the parameter values.

Typically the method includes, in the computer system, displaying an indication of at least one of:

a) the parameter values;

b) the ratio of extra-cellular to intra-cellular fluid; and,

c) an indication of the at least one of the presence, absence or degree of tissue oedema in the subject.

In a second broad form the present invention provides apparatus for detecting tissue oedema in a subject, the apparatus including a processing system for:

a) determining a measured impedance for first and second body segments;

b) for each body segment, and using the measured impedance, determining an index indicative of a ratio of the extra-cellular to intra-cellular fluid;

c) determining an index ratio based on the index for the first and second body segments;

d) determining the presence, absence or degree of tissue oedema based on the index ratio.

Typically the apparatus includes:

a) a current supply for generating an alternating current at each of a plurality of frequencies;

b) at least two supply electrodes for applying the generated alternating current to a subject;

c) at least two measurement electrodes for detecting a voltage across the subject; and,

d) a sensor coupled to the measurement electrodes for determining the voltage, the sensor being coupled to the processing system to thereby allow the processing system to determine the measured impedances.

Typically the apparatus is adapted to perform the method of the first broad form of the invention.

In a third broad form the present invention provides a method of diagnosing tissue oedema in a body region, the method including:

a) applying an alternating current signal at four or more discrete frequencies;

b) measuring an impedance at each frequency;

c) solving the equation:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$ to obtain parameters R_0, R_∞, τ and α,

where:

Z is the measured impedance at angular frequency ω,

R_0 is the resistance at zero frequency,

R_∞ is the resistance at infinite frequency,

τ is a time constant, and

α has a value between 0 and 1; and

d) using one or more of the parameters R_0, R_∞, τ and α to diagnose tissue oedema in the body region.

Typically the method includes diagnosing tissue oedema by determining the presence, absence or degree of tissue oedema.

Typically the method includes:

a) determining the impedance at four discrete frequencies; and,

b) determining values for the parameters by solving the equation using four simultaneous equations.

Typically the method includes:

a) determining values of one or more of the parameters R_0, R_∞, τ and α for first and second body regions;

b) comparing the results from the first body region with the results from the second body region to obtain an indication of the presence of tissue oedema.

Typically the method includes:

a) comparing the parameters R_0 and R_∞ for each body region; and,

b) indicating tissue oedema if the difference is outside a tolerance determined from a normal population.

Typically the method includes:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $R_i = \frac{R_\infty R_e}{R_e - R_\infty}$; and

b) diagnosing tissue oedema in accordance with the determined index.

Typically the method includes indicating tissue oedema by displaying the indication as a position on a scale.

Typically the method is a method according to the first broad form of the invention.

In a fourth broad form the present invention provides apparatus for detecting tissue oedema, the apparatus including:

a) a current supply for applying an alternating current to an anatomical region at four or more discrete frequencies across a frequency range;

b) a monitor for monitoring the bioelectrical impedance of said region; and

c) a processing system for:

i) analysing the bioelectrical impedance by solving:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$ to obtain parameters R_0, R_∞, τ and α,

where:

Z is the measured impedance at angular frequency ω,

R_0 is the resistance at zero frequency,

R_∞ is the resistance at infinite frequency,

τ is a time constant, and

α has a value between 0 and 1; and

ii) using one or more of the parameters R_0, R_∞, τ and α to provide an indication of tissue oedema.

Typically the current supply includes a proximal electrode and distal electrode in electrical connection with a power source.

Typically the monitor includes a first connection and second connection for location on or near the anatomical region.

Typically the monitor includes display means to display the signals indicative of bioimpedance.

Typically the processing system is suitably programmed to perform analysis of data to provide an indication of the presence of tissue oedema.

Typically the apparatus is adapted to perform the method of the third broad form of the invention.

In a fifth broad form the present invention provides a method of diagnosing tissue oedema in a body region, the method including:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where:

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $R_i = \frac{R_\infty R_e}{R_e - R_\infty}$; and

b) indicating the presence of tissue oedema if there is a change in the index R_i/R_e over time.

Typically the method includes:

a) measuring of R_i/R_e is made prior to an event likely to cause oedema; and,

b) comparing to a measurement of R_i/R_e made after the event..

Typically the method is a method according to the first or third broad forms of the invention.

In a sixth broad form the present invention provides apparatus for diagnosing tissue oedema in a body region, the apparatus including a processing system for:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where:

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $R_i = \frac{R_\infty R_e}{R_e - R_\infty}$; and

b) indicating the presence of tissue oedema if there is a change in the index R_i/R_e over time.

Typically the apparatus is adapted to perform the method of the fifth broad form of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

An example of the present invention will now be described with reference to the accompanying drawings, in which: -

Figure 1 is a schematic of an example of a theoretical equivalent circuit for biological tissue;

Figure 2 is an example of a locus of impedance known as a Cole-Cole plot;

Figure 3 is a schematic of an example of a single channel bioimpedance apparatus;

Figure 4 is a schematic of an example of a dual channel bioimpedance apparatus; and,

Figure 5 is a flow chart of an example of a process for evaluating tissue oedema.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 is an example of an equivalent circuit that effectively models the electrical behaviour of biological tissue. The equivalent circuit has two branches that represent current flow through extracellular fluid and intracellular fluid. The extracellular component of biological impedance is represented by R_e and the intracellular component is represented by R_i. Capacitance of the cell membrane in the intracellular path is represented by C.

The relative magnitudes of the extracellular and intracellular components of impedance of an alternating current (AC) are frequency dependent. At zero frequency the capacitor acts as a perfect insulator and all current flows through the extracellular fluid, hence the resistance at zero frequency, R_0, equals R_e. At infinite frequency the capacitor acts as a perfect conductor and the current passes through the parallel resistive combination. The

resistance at infinite frequency is given by $R_\infty = R_iR_e/(R_i+R_e)$. The measured values of R_0 and R_∞ would therefore directly provide the values of R_e and R_i. required for estimation of extracellular water (ECW) and intracellular water (ICW), which lead to identification of oedema by comparison between affected and unaffected body regions. However, as is well known, the practical constraints of skin-electrode impedance do not permit application of DC or very high frequency AC currents, hence the values of the frequencies commonly used can only approximate the ideal measurement frequencies.

The impedance of the equivalent circuit of Figure 1 at an angular frequency ω, where $\omega=2\pi$*frequency, is given by:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1+(j\omega\tau)} \qquad (1)$$

where:

$R_\infty=R_iR_e/(R_i+R_e)$,

$R_0=R_e$ and,

τ is the time constant of the capacitive circuit.

These values can be estimated by extrapolating what is known as a Cole-Cole plot, which is a plot of the vector sum of the resistance R and reactance X that sum to impedance Z. A Cole-Cole plot of reactance against resistance is shown in Figure 2 with an impedance vector Z at a given frequency.

It is also known that biological specimens deviate from the equivalent circuit because the cell membrane is an imperfect capacitor and there is a large variation between cell types in the current path. This results in a Cole-Cole plot of a biological specimen having a depressed centre compared to the equivalent circuit plot shown in Figure 2. A more accurate expression for impedance in a biological sample is therefore given by:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1+(j\omega\tau)^{(1-\alpha)}} \qquad (2)$$

where α has a value between 0 and 1 and can be thought of as an indicator of the deviation of a real system from the ideal model.

Another important value is the impedance Z_c at the peak of the locus in Figure 2. This peak occurs when $\omega = 1/\tau$, which is referred to as the characteristic angular frequency, ω_c which equals $2\pi f_c$.

As explained above, the prior art approach to determining the desired values of R_0 and R_∞ has been to make impedance measurements at multiple frequencies and to construct a section of a Cole-Cole plot. The plot can be extrapolated to determine R_0, R_∞ and Z_c. This procedure takes a significant amount of processing time and therefore makes real time monitoring of bioimpedance problematic. Furthermore, the measurements require determination of both phase and amplitude values which require relatively sophisticated, and therefore expensive, equipment.

Equation (2) has four, unknowns, R_0, R_∞, τ and α. The values of these unknowns can be determined by taking measurements at four discrete frequencies, and solving four simultaneous equations. Any of the established methods such as matrix inversion or numerical iteration can be used to solve the equations for the unknown values.

The values determined by this process compare favourably with the values obtained by the conventional curve fitting technique, in which measured impedances are used to plot a locus similar to that shown in Figure 2, thereby allowing values of R_0 and R_∞ to be obtained.

Greater, accuracy can be achieved by taking measurements at a larger number of frequencies, albeit at a cost in processing overhead. Furthermore, accurate results can usefully be derived by selecting discrete frequencies that span the range of frequencies normally used in multiple frequency bioelectrical impedance analysis (5KHz to 1000KHz).

Once the values of R_0, R_∞ and Z_c are determined they can be used in various ways to detect and quantify oedema in a body region. One approach to this quantification is to compare measurements taken at a first body region against measurements taken at a second body region.

The second measurements may be taken in a paired unaffected body region. For example, a first measurement may be made at a location on the left leg and a second measurement made at the same location on the right leg of the same patient where the right leg is unaffected by

tissue oedema. It is clear to a skilled addressee that other paired anatomical regions may be similarly used when performing the above described methodology. For example, paired areas of the thorax may be assessed.

It is, however, possible to take the second measurement at a dissimilar body region. For example, the first reading may be taken on a leg, and a second reading may be taken on an arm. The analysis of these readings will necessarily involve some different considerations. Again, it is clear to a skilled addressee that a wide range of dissimilar anatomical structures may be used for these measurements, such as a leg and the chest wall. This form of the method is of particular use where two paired anatomical sites are both affected by tissue oedema. The comparison of readings taken in two such affected sites will be distorted and will not produce a reliable indicator of tissue oedema.

As a further alternative, the method may be applied to two or more measurements on the same anatomical region of a subject where those readings are separated in time. For example, a series of readings may be taken on a single limb prior to and subsequent to surgery with a known risk of lymphoedema as a side effect. Analysis of any two or more readings may indicate the early stage of developing lymphoedema and thereby provide a distinct advantage in that the prognosis may be greatly improved by early and aggressive therapeutic intervention. This technique may also be used to monitor the progress of oedema with comparison made between measurements of an affected site.

In the case of comparison of any two dissimilar regions it is known that a correcting factor may be required. A correcting factor may be established by surveying a population of clinically unaffected subjects:

Another approach is a modification of the technique described in a publication, (Cornish, B.H.; Thomas B.J.; Ward L.C.; Angiology Vol 53, No 1, pp 41-47 2002). In this approach the measured parameters are used to calculate an index Ri/Re. as indicative of the ratio of extracellular fluid to intracellular fluid. The extracellular fluid resistance Re is determined from

$$R_e = R_0$$

and intracellular fluid resistance R_i is determined from

$$R_i = \frac{R_\infty R_e}{R_e - R_\infty}$$

Thus, the index *I*, which is indicative of the ratio of extra- to intra-cellular fluid is given by the equation:

$$I = \frac{R_i}{R_e} = \frac{R_\infty}{R_0 - R_\infty} \qquad (3)$$

This approach has particular application to monitoring oedema overtime as a plot of the index against time can disclose the onset and rate of advance of oedema.

Referring to Figure. 3, there is shown a schematic of an apparatus for measuring impedance, including an oscillator 20, divider 21 and filter 22 connected in series to produce alternating current at a number of discrete frequencies when connected to a power, source (not shown). The alternating current passes through cable 23 to electrode 24 through intervening tissue (not shown) to electrode 25, which is connected to a reference 26 via cable 27.

Monitoring electrodes 28, 29 are in connection with bioimpedance measuring meter 30 via cables 31, 32. Signals from bioimpedance measuring meter 30 are passed to analogue/digital converter 33, which is in signal connection with data storing unit 34, which retains the digitised reading of bioimpedance.

The applied signal is suitably derived from a constant current source to ensure that the generated current does not exceed the Australian Standard of a maximum of 32V and a maximum current of 100μA at 10 kHz. The current limit increases to an upper threshold of 1mA at 1000kHz. The applied signal could be derived from a constant voltage source rather than a constant current source providing a mechanism is provided to maintain the safety standard.

A first reading of bioelectrical impedance is taken from a first anatomical region of a subject and stored in data storing unit 34.

The processor 35 calculates the values R_0, R_∞, τ and α by solving the equation (2) and transfers the result to second data storing unit 36. The values may also be presented on display 37.

The processor may also calculate an indicator of oedema, such as the R_i/R_e index, and display this on a scale with a movable indicator. There may also be a simple series of lights which, when illuminated, indicate any one of "unaffected", "possibly affected" or "affected". The display may be any other suitable form of indicator.

It is more convenient for many of the techniques for assessing oedema to use a two-channel bioimpedance meter as shown in Figure 4. In this case, current is passed between the electrodes 24, 25 on, for example, one arm 47 and between the electrodes 24A, 25A on the opposite arm 48. This can be achieved either sequentially, for example through the use of multiplexing, or simultaneously. Monitoring electrodes 28, 29 on the first arm 47 measure bioelectrical impedance while monitoring electrodes 28A, 29A measure bioelectrical impedance on the opposite arm 48. A measuring meter 30 has two channels for simultaneously monitoring signals provided from the monitoring electrodes 28, 29; 28A; 29A. The signals are passed through an analogue/digital converter 33 and then analysed by processor 35. The results are stored in memory 36 and shown on display 37.

Accordingly the processor 35 operates to analyse the impedance signals and use this to provide an evaluation of the presence, absence or degree of tissue oedema. This is typically performed in accordance with applications software provided in the memory. It will be appreciated from this that the processor 35, the memory 36 and the display 37 may typically be formed from a processing system, such as a computer system, computer server, desktop computer, lap-top, specialised hardware, or the like.

An example of the process for monitoring the impedance signals and evaluating tissue oedema will now be described with reference to the flowchart shown in Figure 5.

In particular, at step 600, the impedance at first and second body segments are measured using the apparatus shown in Figure 4. In this example, the body segments are different body segments and may include for example an arm and a leg.

At step 610 the processor 35 determines values of R_0 and R_∞ for each body segment. This can be achieved using a number of mechanisms. For example, given that there are four unknown parameters R_0, R_∞, τ, α, the equation (2) can be used to determine four simultaneous equations, which can then be solved using appropriate mathematical techniques. Alternatively, the measured impedance values can be plotted to derive an arc similar to that shown in Figure 2, which then further allows the values of R_0 and R_∞ to be determined. Alternative techniques may also be used.

At step 620 the values of R_0 and R_∞ are used to determine an index I for each body segment. The index is based on the ratio of the extracellular to intracellular fluid and is therefore calculated using equation (3).

At step 630 an index ratio IR based on a ratio of the first body segment index I_1 to second body segment index I_2 is calculated, with this being used in evaluating the presence, absence or degree of oedema.

This is possible, as, for a healthy subject, there is generally a degree of similarity of intra- and extra-cellular fluid levels, even between different body segments. Thus, for example, if the subject is suffering from a condition other than oedema, which causes a general change in the ratio of extra- to intra- cellular fluid, then this should affect all body segments roughly equally. As a result, assuming that neither body segment has tissue oedema, then the index ratio IR should remain relatively constant for a given individual.

It will be appreciated that in the event that the properties of each body segment are equal, then the index ratio should have a value in the region of 1. Typically however, minor variations in tissue will occur between different body segments, and this can be accounted for in one of two ways.

Firstly, as shown at step 640, the index ratio IR can be compared to a predetermined range. In this case, the range is used to account for variations between body segments that are not attributable to tissue oedema. It will therefore be appreciated that the range is therefore typically set to take into account the difference in index ratio IR between different body portions in a number of different subjects. This range can therefore be set based on data collected from a number of healthy subjects.

In any event, if the index ratio *IR* falls outside the predetermined range, then this is used by the processor 35 to determine that tissue oedema is present in one of the body segments at step 650.

Furthermore, an assessment of the value of the index ratio *IR* can be used in assessing the degree of tissue oedema. Thus, for example, a number of value ranges can be defined, with each range corresponding to a different degree of oedema. In this instance, the processor 35 determines within which range the index ratio *IR* falls, and uses this to generate an indication of the likely degree of tissue oedema.

The value of the index ratio *IR* will also depend on the body segments that have been selected and accordingly, in general a different range will be selected for the comparison depending on the body segments under consideration.

It will also be appreciated that the index ratio *IR* can be used to indicate in which body segment the oedema is present, and this can be based on whether the index ratio *IR* is greater than or less than 1.

The index ratio *IR* may also depend on a number of factors, such as the subject's age, weight, sex and height, and again a respective range can be selected based on these factors. However, to avoid the need for an assessment of such factors, an alternative process of longitudinal analysis can be performed.

In this case, at step 660 the processor 35 can compare the index ratio *IR* to previously determined index ratios IR_{prev} measured for the same subject, on the same body segments. In this situation, the previously determined index ratios IR_{prev} are preferably determined prior to the onset of oedema but this is not essential.

In any event, previous measurements of the same body segments on the same subject will automatically account for inherent variations in tissue properties, which in turn cause different values for the ratio of extra- to intra- cellular fluid even if tissue oedema is not present.

In this case, the processor 35 assesses whether the current index ratio *IR* value is different to the previous index ratio IR_{prev}. If there is change in the value, then the direction in

change in value can indicate either increasing or decreasing levels of tissue oedema, with the magnitude of the change being used to indicate a degree of change at step 650.

In general, at step 650, the display 37 is used to display an indication of one or more of:

- one or more index ratios
- one or more indexes; and,
- the presence, absence or degree of tissue oedema.

It will therefore be appreciated from this that the above-described methodology provides two different methods of determining the onset for oedema. This can be achieved either by performing a longitudinal analysis in which the index ratio *IR* is compared to previously determined index ratios IR_{prev}. Alternatively the index ratio *IR* can be compared to one or more absolute index ratio ranges.

In practice, a combination for the two approaches will generally be used. Thus, for example, when a patient is first admitted for a procedure to be performed, a comparison to absolute index ratio ranges may be used to confirm that it is unlikely that the patient has oedema.

The measured index ratio *IR* can then be used to form the reference value of the index ratio IR_{prev}, allowing subsequent measurements to be compared thereto.

By using the index ratio *IR* described above, this allows variation in tissue properties between different body portions to be taken into account when assessing the presence, absence or degree of tissue oedema, and accordingly, this allows the onset of bilateral oedema to be detected. This is in contrast to previous techniques, in which like body segments are compared. In this case, if impedance measurements of a limb, such as a leg, are compared to measurements from the other corresponding limb, then in the event that oedema is present in both limbs, the impedance measurements will be similar, and will not therefore indicate that oedema is present.

As mentioned above, the values of R_0 and R_∞ can be determined in any one of a number of ways. However, in general it is preferred to be able to determine the values in real-time to thereby vastly enhance the oedema assessment process. In particular, this allows

measurements to be made of the patient, with the processor 35 generating an indication of the degree of tissue oedema in real-time.

The discussion has referred to both oedema and lymphoedema, as it is clear to a skilled addressee that the above method and apparatus may be utilised on any form of tissue oedema. However, it is also likely that the predominant use of the method, and apparatus will be directed mainly to lymphoedema due to its clinical relevance. However, this may change in a specific situation or with time. The method may also be used in comparing a reading from one anatomical region with a separate unpaired region. For example, a reading taken on central localised oedema (eg: ascites) may be referenced against a nonoedematous structure such as a limb.

Throughout the specification, the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. Various changes and modifications may be made to the embodiments described and illustrated without departing from the present invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1) A method of detecting tissue oedema in a subject, the method including, in a processing system:
   a) determining a measured impedance for first and second body segments;
   b) for each body segment, and using the measured impedance, determining an index indicative of a ratio of the extra-cellular to intra-cellular fluid;
   c) determining an index ratio based on the index for the first and second body segments;
   d) determining the presence, absence or degree of tissue oedema based on the index ratio.

2) A method according to claim 1, wherein the method includes, in the processing system:
   a) comparing the index ratio to at least one reference; and,
   b) determining the presence, absence or degree of tissue oedema based on the results of the comparison.

3) A method according to claim 2, wherein the reference includes at least one of:
   a) a predetermined threshold;
   b) a tolerance determined from a normal population; and,
   c) a predetermined range.

4) A method according to claim 2, wherein the reference includes an index ratio previously determined for the subject.

5) A method according to claim 4, wherein the previously determined index ratio is determined prior to the subject undergoing at least one of:
   a) surgery; and,
   b) treatment.

6) A method according to any one of the claims 1 to 5, wherein the first and second body segments are different types of body segment.

7) A method according to any one of the claims 1 to 6, wherein the first and second body segments are limbs.

8) A method according to any one of the claims 1 to 7, wherein the first body segment is a leg and the second body segment is an arm.

9) A method according to any one of the claims 1 to 9, wherein the method includes, in the processing system:

a) determining a plurality of measured impedances for each body segment, each measured impedance being measured at a corresponding measurement frequency; and,

b) determining the index ratio based on the plurality of measured impedances.

10) A method according to claim 9, wherein the method includes, in the processing system:

a) determining values for parameters R_0 and R_∞ from the measured impedance values; and,

b) calculating the index (I) using the equation:

$$I = \frac{R_\infty}{R_0 - R_\infty}$$

where:

R_0 is the resistance at zero frequency; and,

R_∞ is the resistance at infinite frequency.

11) A method according to claim 10, wherein the method includes, in the processing system, determining the parameter values using the equation:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$

where:

Z is the measured impedance at angular frequency ω,

τ is a time constant, and

α has a value between 0 and 1.

12) A method according to claim 11, wherein the method includes, in the processing system:

a) determining the impedance of each body segment at four discrete frequencies; and,

b) determining values for the parameters by solving the equation using four simultaneous equations.

13) A method according to claim 10, wherein the method includes, in the processing system, determining the parameter values by:

a) determining an impedance locus using the measured impedance values; and,

b) using the impedance locus to determine the parameter values.

14) A method according to any one of the claims 1 to 13, wherein the method includes, in the computer system, displaying an indication of at least one of:

a) the parameter values;

b) the ratio of extra-cellular to intra-cellular fluid; and,

c) an indication of the at least one of the presence, absence or degree of tissue oedema in the subject.

15) Apparatus for detecting tissue oedema in a subject, the apparatus including a processing system for:

a) determining a measured impedance for first and second body segments;

b) for each body segment, and using the measured impedance, determining an index indicative of a ratio of the extra-cellular to intra-cellular fluid;

c) determining an index ratio based on the index for the first and second body segments;

d) determining the presence, absence or degree of tissue oedema based on the index ratio.

16) Apparatus according to claim 15, wherein the apparatus includes:

a) a current supply for generating an alternating current at each of a plurality of frequencies;

b) at least two supply electrodes for applying the generated alternating current to a subject;

c) at least two measurement electrodes for detecting a voltage across the subject; and,

d) a sensor coupled to the measurement electrodes for determining the voltage, the sensor being coupled to the processing system to thereby allow the processing system to determine the measured impedances.

17) Apparatus according to claim 15 or claim 16, wherein the apparatus is adapted to perform the method of any one of the claims 1 to 14.

18) A method of diagnosing tissue oedema in a body region, the method including:

a) applying an alternating current signal at four or more discrete frequencies;

b) measuring an impedance at each frequency;

c) solving the equation:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$ to obtain parameters R_0, R_∞, τ and α,

where:

Z is the measured impedance at angular frequency ω,

R_0 is the resistance at zero frequency,

R_∞ is the resistance at infinite frequency,

τ is a time constant, and

α has a value between 0 and 1; and

d) using one or more of the parameters R_0, R_∞, τ and α to diagnose tissue oedema in the body region.

19) A method according to claim 18, wherein the method includes diagnosing tissue oedema by determining the presence, absence or degree of tissue oedema.

20) A method according to claim 18 or claim 19, wherein the method includes:

a) determining the impedance at four discrete frequencies; and,

b) determining values for the parameters by solving the equation using four simultaneous equations.

21) A method according to any one of the claims 18 to 20, wherein the method includes:

a) determining values of one or more of the parameters R_0, R_∞, τ and α for first and second body regions;

b) comparing the results from the first body region with the results from the second body region to obtain an indication of the presence of tissue oedema.

22) A method according to claim 21, wherein the includes:

a) comparing the parameters R_o and R_∞ for each body region; and,

b) indicating tissue oedema if the difference is outside a tolerance determined from a normal population.

23) A method according to claim 21 or claim 22, wherein the method includes:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $R_i = \frac{R_\infty R_e}{R_e - R_\infty}$; and

b) diagnosing tissue oedema in accordance with the determined index.

24) A method according to any one of the claims 18 to 23, wherein the method includes indicating tissue oedema by displaying the indication as a position on a scale.

25) A method according to any one of the claims 18 to 24, wherein the method is a method according to any one of the claims 1 to 14.

26) Apparatus for detecting tissue oedema, the apparatus including:

a) a current supply for applying an alternating current to an anatomical region at four or more discrete frequencies across a frequency range;

b) a monitor for monitoring the bioelectrical impedance of said region; and

c) a processing system for:

i) analysing the bioelectrical impedance by solving:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$ to obtain parameters R_0, R_∞, τ and α,

where:

Z is the measured impedance at angular frequency ω,

R_0 is the resistance at zero frequency,

R_∞ is the resistance at infinite frequency,

τ is a time constant, and

α has a value between 0 and 1; and

ii) using one or more of the parameters R_0, R_∞, τ and α to provide an indication of tissue oedema.

27) Apparatus according to claim 26, wherein the current supply includes a proximal electrode and distal electrode in electrical connection with a power source.

28) Apparatus according to claim 26 or claim 27, wherein the monitor includes a first connection and second connection for location on or near the anatomical region.

29) Apparatus according to any one of the claims 26 to 28, wherein the monitor includes display means to display the signals indicative of bioimpedance.

30) Apparatus according to any one of the claims 26 to 29, wherein the processing system is suitably programmed to perform analysis of data to provide an indication of the presence of tissue oedema.

31) Apparatus according to any one of the claims 26 to 30, wherein the apparatus performs the method of any one of the claims 18 to 25.

32) A method of diagnosing tissue oedema in a body region, the method including:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where:

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $Ri = \frac{R\infty R_e}{R_e - R\infty}$; and

b) indicating the presence of tissue oedema if there is a change in the index R_i/R_e over time.

33) A method according to claim 32, wherein the method includes:

a) measuring of R_i/R_e is made prior to an event likely to cause oedema; and,

b) comparing to a measurement of R_i/R_e made after the event..

34) A method according to claim 32 or claim 33, wherein the method is a method according to any one of the claims 1 to 14, or claims 18 to 25.

35) Apparatus for diagnosing tissue oedema in a body region, the apparatus including a processing system for:

a) calculating an index R_i/R_e as indicative of the ratio of extracellular fluid to intracellular fluid;

where:

R_e is the resistance of extracellular fluid determined from $R_e = R_0$; and,

R_i is the resistance of intracellular fluid determined from $Ri = \frac{R\infty R_e}{R_e - R\infty}$; and

b) indicating the presence of tissue oedema if there is a change in the index R_i/R_e over time.

36) Apparatus according to claim 35, wherein the apparatus is for performing the method of any one of the claims 1 to 14, or claims 18 to 25, or 32 to 34.

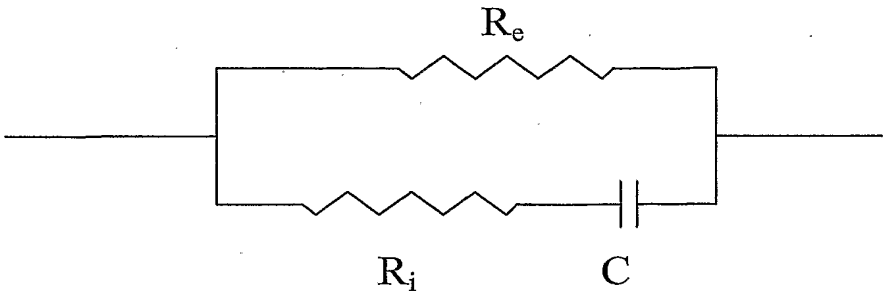

FIG 1

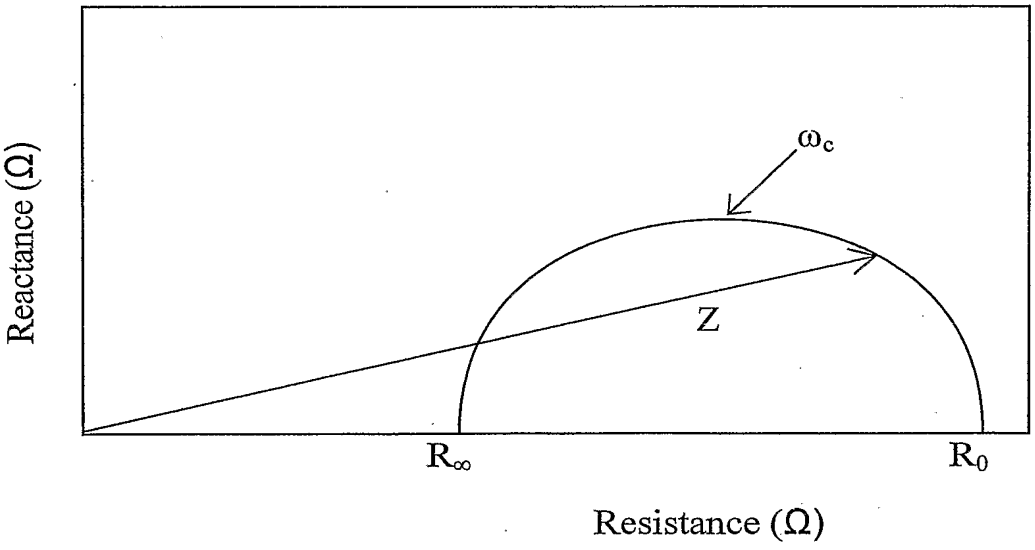

FIG 2

FIG. 3

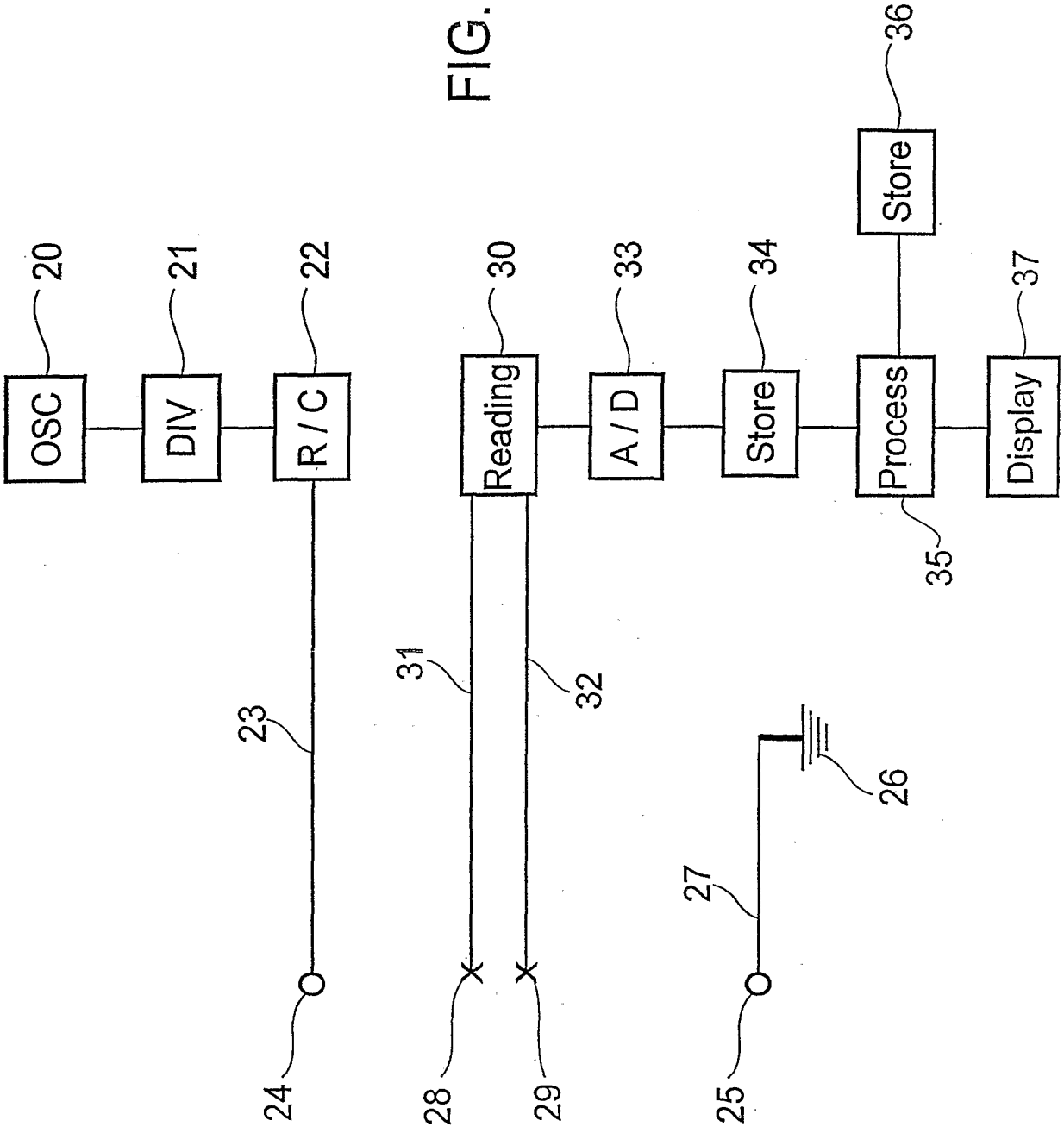
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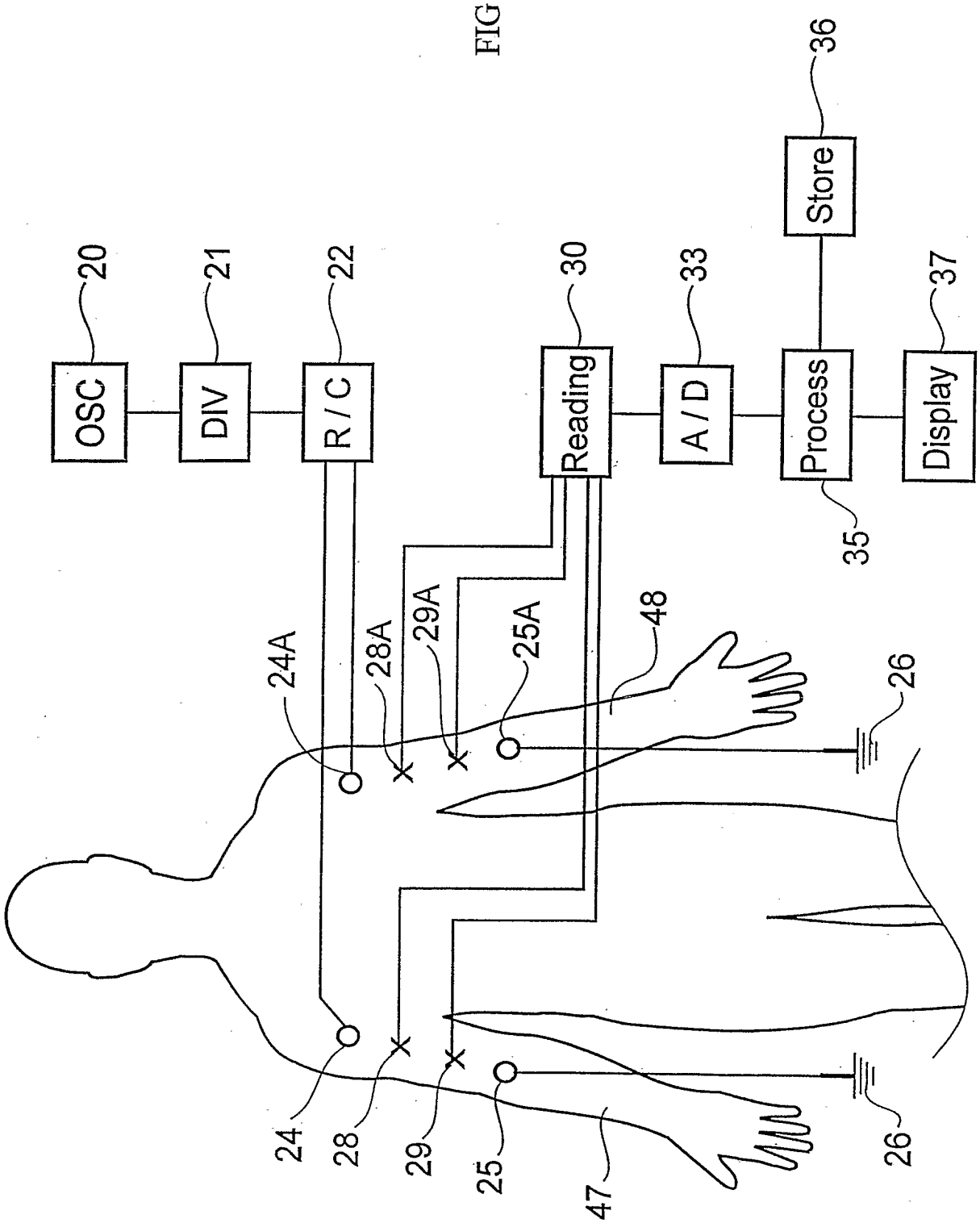
FIG 4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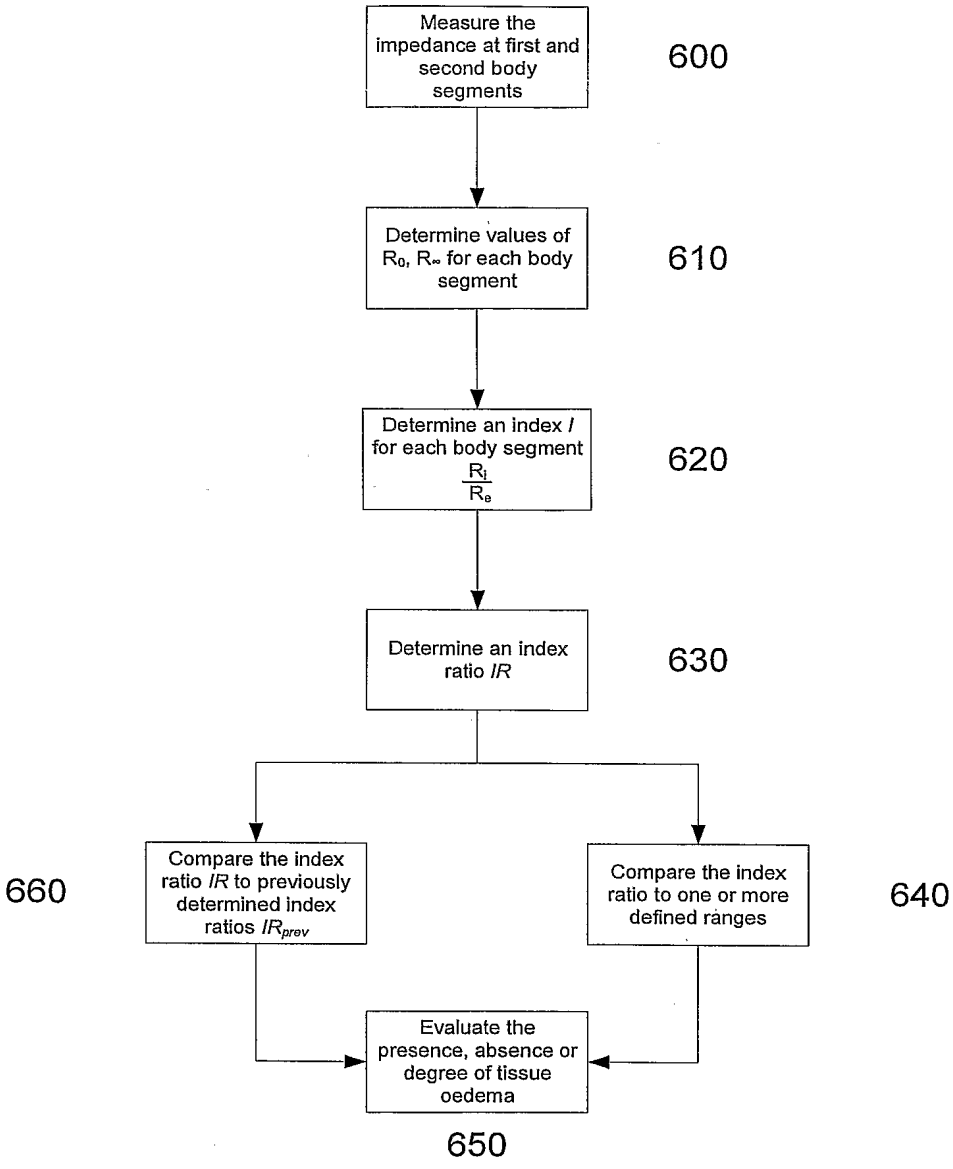
Measure the impedance at first and second body segments
600
Determine values of R_0, R_∞ for each body segment
610
Determine an index *I* for each body segment $\frac{R_i}{R_e}$
620
Determine an index ratio *IR*
630
Compare the index ratio *IR* to previously determined index ratios IR_{prev}
660
Compare the index ratio to one or more defined ranges
640
Evaluate the presence, absence or degree of tissue oedema
650

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000876

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61B 5/053

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI and keywords: oedema and impedance and body and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/0020138 A1 (ISHIGOOKA et al.) 6 September 2001 Paragraphs 8 to 10, 62 to 69 and 71 to 85	1 - 36
X	US 6151523 A (ROSELL FERRER et al.) 21 November 2000 Column 1 line 35 to column 2 line 3 Column 6 lines 1 to 54	1 - 36
X	US 6496725 B2 (KAMADA et al.) 17 December 2002 Column 7 line 50 to column 8 line 13 Column 6 line 52 to column 7 line 8	1 - 36
X	US 6643543 B2 (TAKEHARA et al.) 4 November 2003 Column 1 lines 10 to 24 Column 7 lines 24 to 53	1 - 36

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2005	- 6 JUL 2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000876

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/0161311 A1 (WARD et al.) 31 October 2002 Whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2005/000876

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	2001020138	EP	1118308	JP	2001198098	US	6714813
US	6151523	EP	0865763	ES	2151774		
US	6496725	CN	1308920	EP	1112715	JP	2001187035
		US	2001007924				
US	6643543	EP	1177760	JP	2002045346	US	2002022787
US	2002161311	AU	52029/00	CA	2375249	EP	1196766
		US	6760617	US	2004186392	WO	0079255

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX